

EXHIBIT 18

National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains

M. Kit Delgado, MD, MS*; Yanlan Huang, MS; Zachary Meisel, MD, MS; Sean Hennessy, PharmD, PhD; Michael Yokell, MD; Daniel Polsky, PhD; Jeanmarie Perrone, MD

*Corresponding Author. E mail: kit.delgado@uphs.upenn.edu, Twitter: @kit_delgadoMD.

Study objective: To inform opioid stewardship efforts, we describe the variation in emergency department (ED) opioid prescribing for a common minor injury, ankle sprain, and determine the association between initial opioid prescription intensity and transition to prolonged opioid use.

Methods: We analyzed 2011 to 2015 US private insurance claims (Optum Clinformatics DataMart) for ED-treated ankle sprains among opioid-naïve patients older than 18 years. We determined the patient- and state-level variation in the opioid prescription rate and characteristics, and the risk-adjusted association between total morphine milligram equivalents (MMEs) of the prescription and transition to prolonged use (filling 4 or more opioid prescriptions 30 to 180 days after the index visit).

Results: A total of 30,832 patients met inclusion criteria. Of these patients, 25.1% received an opioid prescription with a median total MME of 100 (interquartile range 75 to 113), tablet quantity of 15 (interquartile range 12 to 20), and days supplied of 3 (interquartile range 2 to 4). State-level prescribing rates ranged from 2.8% in North Dakota to 40.0% in Arkansas. Among patients who received a total MME of greater than 225 (equivalent to >30 tabs of oxycodone 5 mg), the adjusted rate of prolonged opioid use was 4.9% (95% CI 1.8% to 8.1%) compared with 1.1% (95% CI 0.7% to 1.5%) among those who received at total MME of 75 and 0.5% (95% CI 0.4% to 0.6%) among those who did not fill an opioid prescription.

Conclusion: Opioid prescribing for ED patients treated for ankle sprains is common and highly variable. Although infrequent in this population, prescriptions greater than 225 MME were associated with higher rates of prolonged opioid use. This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing. [Ann Emerg Med. 2018;■:1-12.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

The US opioid epidemic claimed 42,249 lives in 2016.¹ In response, many states and some health insurers and pharmacy chains have enacted policies limiting the duration of new opioid prescriptions for acute pain conditions.²⁻⁴ In the early part of 2018, Congress introduced the Comprehensive Addiction and Recovery Act 2.0, a bipartisan bill that includes a 3-day-supply limit on all new opioid prescriptions. The goal of opioid stewardship and prescription limit policies is to reduce the potential for transition to prolonged use, potential misuse, and diversion of unused tablets. Despite recent policy action, the scientific evidence base on the threshold prescription-intensity-associated

increased risk of transition to prolonged use and misuse is limited.

Importance

Previous studies have found an association between increasing opioid prescription duration or intensity and transition to prolonged use, but were not designed to account for differences in the indication for the initial prescription.⁵⁻⁷ This is problematic because the onset of some pain conditions, such as acute lumbar radiculopathy, often leads to chronic pain. Therefore, it cannot be determined whether prolonged use is due to the development of opioid dependence after the initial prescription or to the independent development of increased pain sensitivity (hyperalgesia), a chronic pain

Editor's Capsule Summary*What is already known on this topic*

Opioid use disorder may start with treatment of a self-limiting event.

What question this study addressed

How often is an opioid prescribed and what use exists later after emergency department (ED) care for an isolated ankle sprain?

What this study adds to our knowledge

In greater than 30,000 single-insurer-paid ED encounters, 25% of patients received an opioid prescription with a median 15 tablets, with wide variation across the United States (range by state of 3% to 40%). Patients receiving more opioid at ED discharge had higher rates of prescriptive opioid use after 30 days.

How this is relevant to clinical practice

These observations do not prove a causal link between acute care opioid exposure and longer use.

syndrome, or other factors. A second issue with current prescription limits is that basing policy on days supplied is imprecise. A common dosing order for oxycodone 5 mg is to receive 1 to 2 tablets every 4 to 6 hours as needed for pain. With these instructions, a 7-day prescription could vary anywhere from 1 tablet to 84 tablets, or 7.5 to 630 morphine milligram equivalents (MMEs).⁸ Therefore, the effect of policies to limit the days supplied on reducing the total number of opioid tablets and MMEs entering the community remains unclear, particularly if clinicians respond by writing for the same number of tablets but to be received during fewer days.

Goals of This Investigation

To guide opioid stewardship efforts by benchmarking variation in prescribing and to generate clearer evidence on the risks of features of initial opioid prescriptions, we analyzed commercial insurance claims from opioid-naïve patients treated in the emergency department (ED) for ankle sprains. We chose this indication and setting for 3 reasons. First, ankle sprains are common minor injuries for which pain rapidly improves within 2 weeks.⁹ Therefore, any risk of subsequent opioid misuse is likely to outweigh the treatment benefit, given that nonopioid analgesics have been found to be equally effective for acute pain management.^{10,11} Second, although initial opioid

prescriptions written in the ED are more consistent with current prescribing guidelines than those from non-ED settings and are typically for smaller quantities (and thus patients receiving them are less likely to progress to long-term use), EDs remain a common source of acute opioid prescriptions.^{12,13} Third, there is still significant variability in opioid prescribing by emergency physicians, and patient assignment is essentially random.^{6,13} This represents an opportunity for quality improvement and also reduces the potential bias of downstream prescriptions' being associated with characteristics of the initial prescriber.

We sought to determine the degree of patient- and state-level variation in opioid prescribing in this setting and the association between the variation in MMEs prescribed and transition to prolonged opioid use. We hypothesized variation in prescribing would be substantial and that larger opioid prescriptions would be associated with higher likelihood of prolonged use.

MATERIALS AND METHODS**Selection of Participants**

We used a cohort study design in a retrospective analysis of the Clinformatics Data Mart Database (OptumInsight), which is composed of administrative claims of 13 million privately insured enrollees throughout the United States.¹⁴⁻¹⁶ This population is similar to the US population of commercially insured people in age, race or ethnicity, and sex and has a median continuous enrollment period of 24 months.¹⁶

We identified all index ED encounters for ankle sprains in patients older than 18 years that occurred from January 1, 2011, to December 31, 2015. The index visit was defined as the earliest visit in which the enrollee had a provider claim by an emergency physician with a place-of-service designation in the ED and a diagnosis code of ankle sprain (*International Classification of Diseases, Ninth Revision [ICD-9]* code 845.00 to 845.09 and *ICD-10* S93.4). We excluded patients who had any other injury diagnoses as defined by State and Territorial Injury Prevention Directors Association consensus definitions¹⁷⁻¹⁹ and those who had recurrent visits for ankle sprain during the study period to decrease the likelihood that future prescriptions were associated with a more severe initial presentation. To restrict the study population to patients who were likely to be prescription opioid naïve, we excluded all those who were not continuously enrolled for 6 months before the index ED visit and those who had filled an opioid prescription in these previous 6 months.^{6,12}

We identified prescription claims corresponding to an opioid according to National Drug Codes (excluding methadone and non-tablet formulations) filled within 3 days

of the index ED visit. We excluded any encounters for patients who had intervening medical claims for ankle sprains within 3 days of the ED visit.

Outcome Measures

The primary outcome was opioid prescription rate, defined as the proportion of adult opioid-naïve patients treated for ankle sprains who filled an opioid prescription within 3 days of the ED visit. Secondary outcomes included characteristics of the initial prescription and continued opioid use beyond the initial prescription.

Characteristics of the initial prescription included number of tablets, days supplied, and MMEs per prescription.²⁰ The days supplied on the pharmacy prescription claims are entered at the point of sale by the pharmacist according to dosing instructions and number of tablets dispensed (personal communication, James A. Schaeffer, Health Informatics, Optum, July 2017).

We measured prolonged opioid use in the 30 to 180 days after the index ED visit, given that pain from ankle sprains rapidly improves within 2 weeks.⁹ We defined prolonged use as filling 4 or more subsequent opioid prescriptions during this period^{21,22} and used alternative specifications in our sensitivity analyses. We limited the follow-up period to 6 months to reduce the likelihood of survivor bias, as the development of an opioid use disorder is associated with losing employment and, thus, employer-based private insurance.^{23,24} Indeed, in our final study sample the insurance enrollment attrition rate between 6 and 12 months of follow-up was 1.5% (95% confidence interval [CI] 0.4% to 2.5%) higher among patients who were prescribed opioids (16.7%) compared with those who did not fill opioid prescriptions (15.2%). To further validate our outcome, we tabulated the most common first listed medical diagnosis codes within the 7 days before new opioid prescription fills 30 to 180 days after the index encounter. This analysis allowed us to explore the extent to which new prescriptions could be attributed to persistent ankle pain rather than another condition completely unrelated to the index ankle sprain.

We extracted information on patients' age, sex, highest level of education, and race. We also identified the patients' Elixhauser comorbidities, as well as diagnosis codes for drug abuse, alcohol abuse, depression, and psychoses as gathered from diagnosis codes on the index ED visit and any medical claims filed in the previous 6 months.²⁵

Primary Data Analysis

First, we tabulated patient characteristics according to whether an opioid prescription was filled or not. Among those who filled opioids, we stratified patient characteristics

according to whether a prescription was above or below the median total MME prescribed in the sample. We compared the magnitude of differences in patient and prescription characteristics between groups by using 95% CIs for the differences.

Second, we described the variation in the opioid prescription rate and characteristics at the patient and state level and over time. Prescriptions were aggregated by state according to the state associated with the prescribers' deidentified National Provider Identifier number.

Third, we calculated the patients' expected probability of receiving an opioid prescription by using a logistic regression model adjusting for age; sex; highest level of education; race; the total number of Elixhauser comorbidities; a history of drug abuse, alcohol abuse, depression, or psychosis; and year. We then estimated observed to expected state-level prescribing ratios with 95% CIs, with values greater than 1 indicating that patients in that state were more likely than expected to fill opioid prescriptions, and those less than 1 indicating that patients in that state were less likely than expected to fill opioid prescriptions.²⁶ For the state level analyses limited to those treated in 2014-15, we excluded states with fewer than 25 patients in the study sample.

Fourth, we quantified the number of tablets that would be prevented from entering the community from reducing excessive variation by (1) reducing all states with above-median opioid prescribing rates to the median rate for ankle sprains; and (2) leveling all above-median opioid prescriptions supplies for ankle sprains to the median.

Fifth, we quantified the association between the initial MME prescribed among patients who filled a prescription and prolonged use. MME cutoffs were selected according to common tablet quantities dispensed for the most potent opioid prescribed, oxycodone 5 mg: 1 to 75 MMEs (<10 tablets), 76 to 150 MMEs (11 to 20 tablets), 151 to 225 MMEs (21 to 30 tablets), and greater than 225 MMEs (>30 tablets). We quantified the association with a logistic regression model adjusting for age; sex; highest level of education; race; the total number of Elixhauser comorbidities; a history of drug abuse, alcohol abuse, depression, or psychosis; year; and state. We then performed sensitivity analyses to assess the robustness of our findings, including using tablets dispensed (adjusted for MMEs/tablet) and days supplied as the independent measure of interest; limiting the exposure to just prescriptions for hydrocodone and oxycodone; and considering alternative measures of prolonged use based on the number of prescriptions filled in the follow-up window. The University of Pennsylvania institutional review board determined that this study was eligible for institutional review board exemption. Stata (version 14.1; StataCorp,

College Station, TX) and SAS (version 9.4; SAS Institute, Inc., Cary, NC) were used to conduct the statistical analyses.

RESULTS

Characteristics of Study Subjects

Our sample consisted of 30,832 patients with an ED visit for an isolated injury of ankle sprain who had not filled an opioid prescription in the previous 6 months (Figure 1).

The overall opioid prescribing rate in this sample was 25.1% (n=7,739). Among the 25,849 patients who had continuous enrollment for 6 months after the ED visit, the prescribing rate was similar (25.0%; n=6,463). Demographic and clinical characteristics were similar between patients who were prescribed an opioid versus those who were not, as well as those who received above-versus below-median (100) total MME prescriptions (Table).

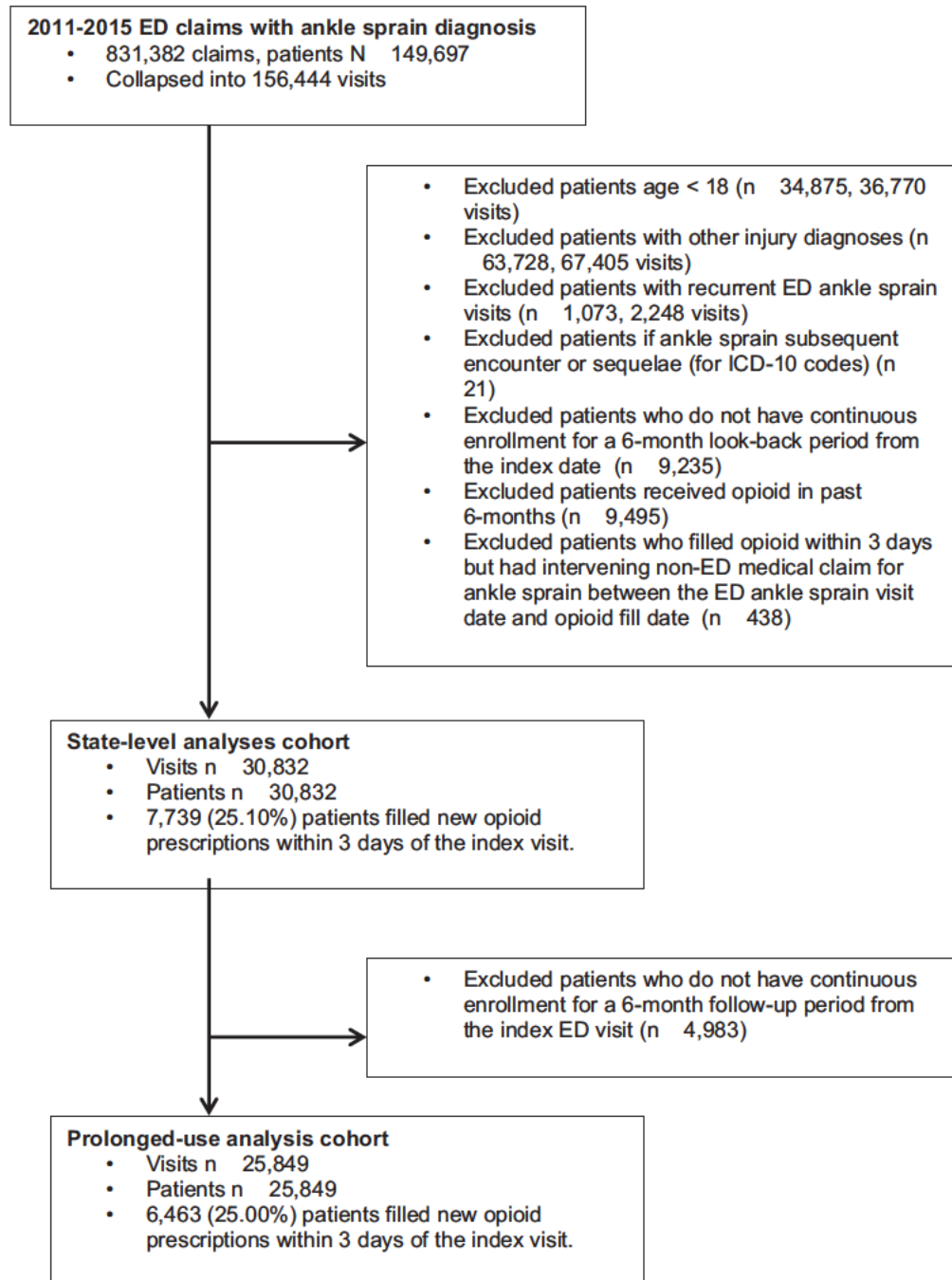


Figure 1. Study sample.

Main Results

Hydrocodone was the most commonly prescribed opioid (64.9%), followed by tramadol (16.2%), oxycodone (14.4%), and codeine (5.5%). The median number of tablets prescribed for all opioid prescriptions was 16, with an interquartile range (IQR) of 12 to 20 tablets. The median total MME was 100 (IQR 75 to 112.5 MMEs) and median days supplied was 3 (IQR 2 to 4 days). However, only 5% of patients who were prescribed opioids were given more than

30 tablets, or greater than 200 MME total (Figure 2). The overall prescription rate declined modestly during the study period, from 28.1% (95% CI 27.1% to 29.1%) in 2011 to 20.4% (95% CI 19.2% to 22.6%) in 2015 (Figure 3A).

State-specific prescription rates varied by a factor of 14.2, ranging from 40.0% in Arkansas to 2.8% in North Dakota, with a national median prescribing rate of 24.1% (Figure 3A). There was less state-level variation in the MMEs per prescription (median 98.9 [range 77.5 to 136.3]) and

Table. Characteristics of opioid-naïve patients treated for ankle sprains.

Patient Characteristics	No Opioid Prescription (n=19,386)	Filled Opioid Prescription (n=6,463)	Filled Opioid Prescription, <100 MMEs (n=4,576)	Filled Opioid Prescription, >100 MMEs (n=1,887)
Median age (IQR), y	39 (25 56)	38 (28 52)	38 (25 52)	40 (29 52)
Women (%)	10,915 (56.3)	3,392 (52.5)	2,492 (54.5)	900 (47.7)
Race/ethnicity (%)				
Non Hispanic white	13,165 (67.9)	4,595 (71.1)	3,235 (70.7)	1,360 (72.1)
Hispanic white	2,073 (10.7)	652 (10.1)	468 (10.2)	184 (9.8)
Black	2,483 (12.8)	826 (12.8)	599 (13.1)	227 (12.0)
Asian	554 (2.9)	116 (1.8)	90 (2.0)	26 (1.4)
Unknown	470 (2.4)	104 (1.6)	70 (1.5)	34 (1.8)
Highest education level (%)				
<12th grade	88 (0.5)	33 (0.5)	23 (0.5)	10 (0.5)
12th grade	5,818 (30.0)	1,960 (30.3)	1,389 (30.4)	571 (30.3)
<Bachelor's	9,723 (50.2)	3,346 (51.8)	2,392 (52.3)	954 (50.6)
>Bachelor's	3,287 (17.0)	1,020 (15.8)	702 (15.3)	318 (16.9)
Unknown	470 (2.4)	104 (1.6)	70 (1.5)	34 (1.8)
Mean No. of Elixhauser comorbidities (SD)	0.98 (1.62)	0.94 (1.52)	0.93 (1.50)	0.97 (1.57)
Hypertension (%)	4,206 (21.7)	1,459 (22.6)	1,004 (21.9)	455 (24.1)
Depression (%)	1,770 (9.1)	629 (9.7)	452 (9.9)	177 (9.4)
Diabetes, uncomplicated (%)	1,708 (8.8)	579 (9.0)	401 (8.8)	178 (9.4)
Chronic pulmonary disease (%)	1,829 (9.4)	563 (8.7)	414 (9.0)	149 (7.9)
Hypothyroidism (%)	1,484 (7.7)	454 (7.0)	321 (7.0)	133 (7.0)
Obesity (%)	943 (4.9)	367 (5.7)	252 (5.5)	115 (6.1)
Cardiac arrhythmias (%)	941 (4.9)	250 (3.9)	172 (3.8)	78 (4.1)
Diabetes, complicated (%)	449 (2.3)	147 (2.3)	101 (2.2)	46 (2.4)
Fluid and electrolyte disorders (%)	503 (2.6)	139 (2.2)	92 (2.0)	47 (2.5)
Renal failure (%)	471 (2.4)	136 (2.1)	89 (1.9)	47 (2.5)
Alcohol abuse (%)	180 (0.9)	73 (1.1)	51 (1.1)	22 (1.2)
Drug abuse (%)	203 (1.0)	73 (1.1)	55 (1.2)	18 (1.0)
Prescription characteristics				
Drug name (%)				
Hydrocodone		4,197 (64.9)	3,267 (71.4)	930 (49.3)
Oxycodone		928 (14.4)	255 (5.6)	673 (35.7)
Codeine		353 (5.5)	272 (5.9)	81 (4.3)
Tramadol		1,050 (16.2)	782 (17.1)	268 (14.2)
Other		8 (0.1)	2	6 (0.3)
Median number of tablets (IQR)		16 (12 20)	15 (12 20)	24 (20 30)
Median days supplied (IQR)		3 (2 4)	3 (2 4)	4 (3 5)

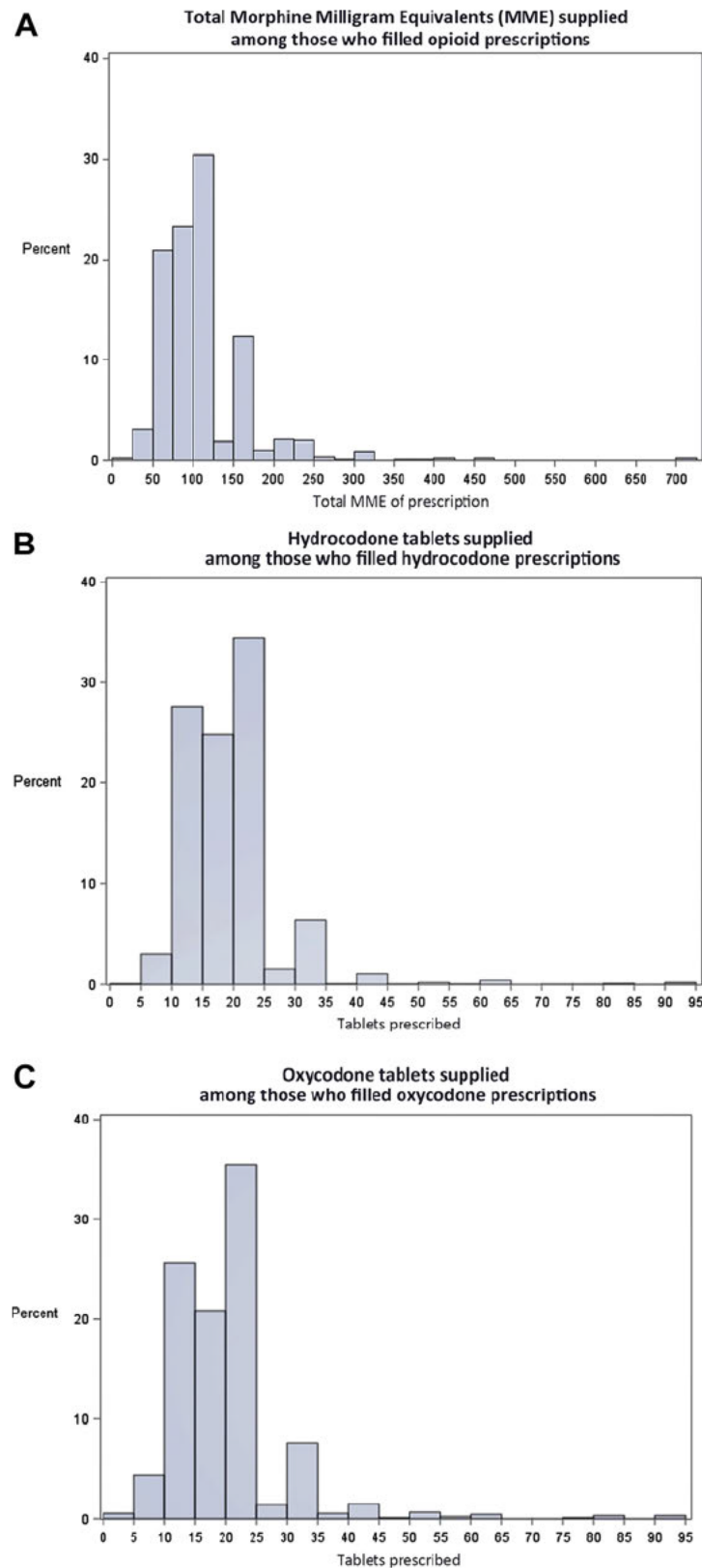


Figure 2. Patient-level variation in the quantity prescribed for opioid-naïve patients with ankle sprains. A, The total MMEs per prescription of all patients who received opioid prescriptions (n=6,464; median=100). B, The number of tablets prescribed for patients who received hydrocodone (n=4,197; median=15). C, The number of tablets prescribed for patients who received oxycodone (n=928; median=16).

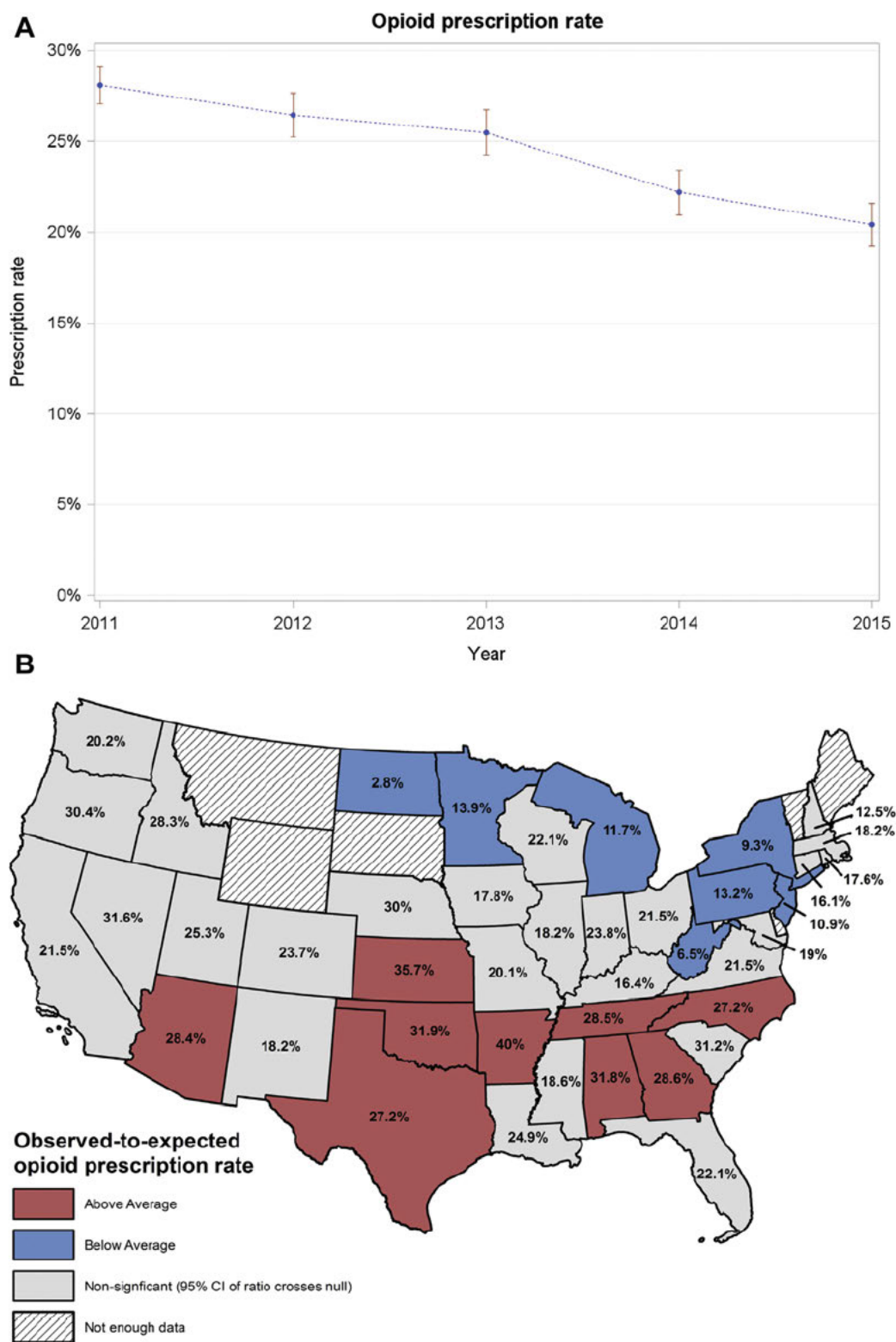


Figure 3. A, The proportion of opioid-naïve patients treated in the ED for ankle sprains who were prescribed opioids according to year of ED visit. The whiskers indicate 95% CIs. B, State-level variation in the ED opioid prescribing rate for ankle sprains in 2014 to 2015 among patients who were opioid naïve. The median state-level prescribing rate during these years was 21.3%. The observed prescribed rate is displayed within each state. States with higher-than-expected prescribing rates based on case mix are highlighted in red and those with lower-than-expected prescribing rates are shown in blue (see Figure E1, available online at <http://www.annemergmed.com>, for caterpillar plot). Case mix was adjusted for age, sex, race, ethnicity, education, comorbid conditions, and year, using multivariate logistic regression.

quantity supplied per patient (median 18.2 [range 13.6 to 40.0]) for patients who received prescriptions. After adjustment for case mix and volume, the prescription rate variation persisted in 2014 to 2015. States in the southern United States accounted for most of the higher-than-expected prescribing rates (Figure 3B, Figure E1 [available online at <http://www.annemergmed.com>]).

There were a total of 143,064 opioid tablets prescribed for patients in the study sample who filled prescriptions. Just reducing the excess variation in the state-level prescription rates by bringing states with above-average prescribing rates to the median of 24.1% would have resulted in the prescribing of 18,260 fewer opioid tablets. On the other hand, reducing the excess variation in prescription quantities by bringing prescriptions above the median to the median of 16 tablets would have resulted in an even bigger reduction, 32,177 fewer tablets prescribed.

Prolonged opioid use (4 or more new opioid prescriptions 30 days after the initial prescription) was slightly higher among patients prescribed any opioid, 0.73% (95% CI 0.63% to 0.84%) versus those who were not prescribed opioids, 0.50% (95% CI 0.40% to 0.59%). Only a small proportion of subsequent prescriptions among patients who went on to high-risk prolonged use were due to first listed diagnoses of nontraumatic joint disorders (7.5%) and sprains and strains (5.8%) of any kind. In contrast, subsequent prescriptions were more likely to be associated with other diagnosis codes (>80%) such as connective tissue disease (7.8%), back problems (5.8%), medical examination (3.6%), headache (2.6%), abdominal pain (2.0%), and urinary tract infections (2.0%) (Table E1 in Appendix E1, available online at <http://www.annemergmed.com>).

After multivariate risk adjustment, the associated probability of high-risk prolonged use among patients who received a total of MME of 75 or less was 1.10% (95% CI 0.72% to 1.53%) and remained similar for those who received up to 225 MMEs. However, above that threshold there was increased association with prolonged use, 4.9% (95% CI 1.8% to 8.1%) (Figure 4A).

When the population was restricted to just patients prescribed the higher-potency drugs, hydrocodone and oxycodone, the dose-response relationship between total MMEs of the initial prescription and high-risk prolonged use was stronger (Figure 4B). Patients prescribed greater than 225 total MMEs in this group had a 6.3% probability (95% CI 2.1% to 10.5%) of developing prolonged use versus those prescribed less than 75 MMEs (1.2%; 95% CI 0.7% to 1.6%).

Female sex, between 35 to 44 years of age, higher comorbidity burden, and history of drug abuse were also independently associated with transition to high-risk

prolonged use (see full model results in Table E1 in Appendix E1, available online at <http://www.annemergmed.com>). Other sensitivity analyses varying alternative ways to measure prolonged use and initial prescription intensity confirmed the robustness of our findings (Appendix E1, available online at <http://www.annemergmed.com>).

LIMITATIONS

There are several limitations to this study. First, unmeasured differences between patients could have accounted for the observed associations. Arguing against this possibility is the observation that, among patients who were prescribed an opioid, measured patient characteristics were not significantly different according to prescription intensity. Furthermore, limiting the population to ankle sprains reduces the possibility that continued use was due to the development of chronic pain because the majority of ankle sprains resolve within 2 to 3 weeks regardless of initial pain severity.⁹ This is supported by the fact that we found that less than 14% of new prescriptions among patients with prolonged use were associated with sprains, strains, and nontraumatic joint pain of any type.

Second, we made the assumption that prescriptions were written for ankle sprains by limiting this analysis to claims with ankle sprains as the only injury diagnosis. It is possible that there were prescriptions for other indications that were not coded. Relatedly, data limitations preclude us from unequivocally attributing the prescription to ED clinicians. We addressed this by excluding patients who had other intervening medical claims for ankle sprains within the 3-day attribution window.

Third, we likely underestimated the opioid prescription rate if some patients filled prescriptions by paying out of pocket instead of using health insurance.²⁷ Finally, if data from 2017 were available and used to replicate this analysis, there might be a lower measured association with prolonged use because of the increase in prescription drug monitoring programs^{28,29} and prescribing guidelines³⁰ and the great increase in the availability and use of low-cost illicit opioids.^{31,32} All these factors increase the likelihood of an earlier transition to illicit opioids rather than the seeking of repeated prescription fills for individuals developing a new opioid use disorder after exposure to a prescription opioid.³³⁻³⁵ Given the recent significant increase in deaths from illicit opioids,³⁶ this further highlights the importance of keeping opioid-naïve patients opioid naïve when possible.

DISCUSSION

In this national study of 30,832 commercially insured, opioid-naïve patients treated in the ED for ankle sprains in 2011 to 2015, we found that opioid prescribing was

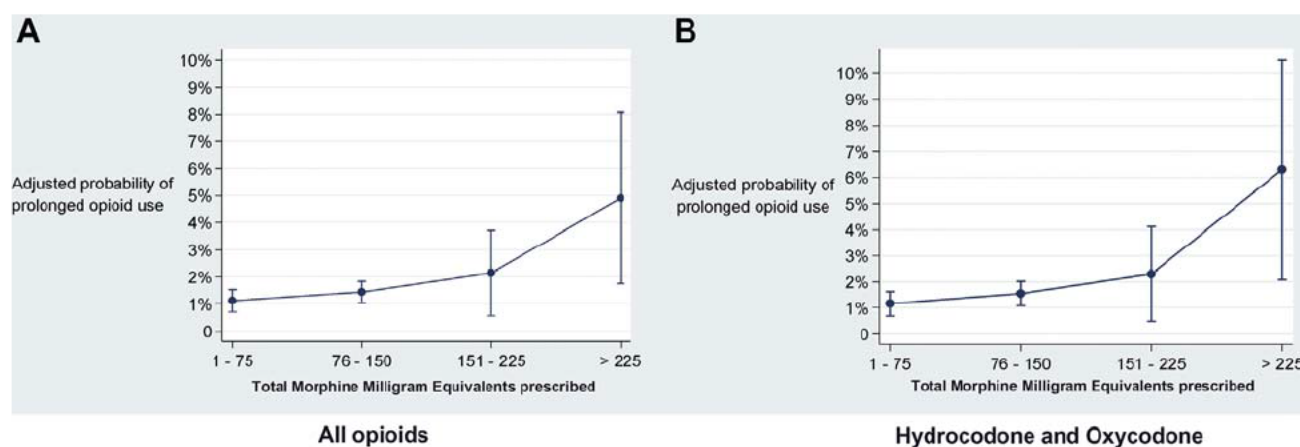


Figure 4. A, Association between total MMEs prescribed and the adjusted probability of filling 4 or more new opioid prescriptions 30 to 180 days after the index visit for ankle sprain among patients who were previously opioid naive. The whiskers indicate 95% CIs. The logistic regression model adjusted for age; sex; race; ethnicity; educational level; Elixhauser comorbidity score; history of drug abuse, depression, and psychoses; state; and year (model area under the curve=0.78). B, The population limited to just patients prescribed hydrocodone and oxycodone (model area under the curve=0.81). For reference, 225 MMEs is the equivalent of 30 tablets of oxycodone 5 mg, and the baseline rate of prolonged use among patients who were not prescribed opioids was 0.5% (95% CI 0.4% to 0.6%). See Appendix E1, available online at <http://www.annemergmed.com>, for full model estimates and sensitivity analyses of model specifications and outcomes.

common and that there was significant patient- and state-level variation in prescribing patterns. Although prescribing is declining, 20% of opioid-naïve ankle sprain patients were prescribed opioids in 2015, and the prescribing rate was greater than 10 times higher in some states versus others. This is concerning because ankle sprains are a minor, self-limited condition for which there is likely to be little clinical benefit from opioids.¹⁰

Although there was significant variation in the intensity of prescriptions written, less than 5% of them were written above a clinically significant threshold of more than 225 MMEs. We found that prescriptions above this threshold were associated with nearly a 5-fold increased probability of transition to prolonged use. The interpretation of this finding is that for approximately every 26 patients exposed to greater than 225 MMEs (the equivalent of more than 30 tablets of oxycodone 5 mg) instead of 75 MMEs or less (equivalent to 10 tablets of oxycodone 5 mg), one additional patient transitioned to prolonged use. Although there is room for improvement in promoting opioid stewardship for this minor condition in the ED, the majority of prescriptions written were concordant with guidelines for a 3-day supply^{12,13,30} and had a low total MME of 100 or less. Therefore, more research is urgently needed to examine the relationship between total MMEs, prolonged use, and adverse events in other contexts, such as for postoperative pain, in which prescriptions are much larger.¹²

Our findings make several novel contributions to the increasing understanding of opioid prescribing and downstream risks. First, this analysis addresses limitations

of previous analyses,⁵⁻⁷ in which prolonged opioid use could be caused by the development of a new chronic pain condition at the index prescription. By focusing on ankle sprains, an isolated acute injury that is readily apparent on examination and that rapidly improves within 2 weeks,⁹ we decreased the likelihood that future opioid prescriptions beginning 1 month after injury were related to the index condition for which the original opioid was prescribed. Nonsteroidal anti-inflammatory drugs rather than opioids are first-line treatment for ankle sprains^{37,38} and are just as effective as opioids for pain reduction.¹⁰ We confirmed that the majority of subsequent prescriptions were unlikely to be related to the initial ankle sprain or chronic ankle pain. This suggests that association between larger prescriptions and increased likelihood of prolonged use could be due to other factors such as patients requesting opioids as default pain control, or the development of dependence or misuse. More research is needed to better understand the underlying mechanisms between exposure to larger prescriptions and increased downstream prescription fills. Furthermore, our study population, with a median age of 39 years, was younger than previous populations that have been studied.⁵⁻⁷ For example, a previous rigorously conducted study using Medicare data⁶ may have underestimated the relationship between initial prescription and long-term use because opioid prescriptions carry increased acute adverse effects for elderly patients and are generally prescribed with more caution in this population.³⁹ Additionally, younger and middle-aged populations are at highest risk of developing a new opioid

use disorder after exposure to opioid prescriptions,^{40,41} and of diverting unused tablets.⁴²

Although our study was not designed to evaluate the association between being prescribed any opioid and prolonged use, our findings that patients prescribed opioids were more likely to go on to prolonged use compared with those who did not fill opioids are consistent with those of previous research^{6,7,43,44} and support the importance of keeping opioid-naïve patients opioid naïve.

Second, our study contributes actionable evidence for policymakers, health systems, and clinicians. The significant statewide variation in ED ankle sprain opioid prescribing rates, with a concentration of higher prescribing in the southern United States, is consistent with geographic variation in prescribing for all indications.⁴⁵ By limiting this analysis to a single minor condition for which opioids are not first-line treatment, and adjusting for case mix, our study suggests ample opportunity to reduce excessive prescribing. More than 140,000 opioid tablets could have been prevented from entering the community if opioids had not been prescribed for our study sample. Substantial reductions in tablets being prescribed could be accomplished with efforts aimed at decreasing excessive variation in the prescribing rate and quantity supplied. This study demonstrates how well-defined prescribing indications can be used to promote benchmarks for opioid stewardship efforts. More research is needed to understand the patient, clinician, and environmental causes of this geographic variation and its contributions to the opioid epidemic.

Despite the fact that most current guidelines and prescription limit policies are written in regard to days supplied, there is a lack of specificity about how many tablets and MMEs of common opioid prescriptions such as hydrocodone or oxycodone constitute a day's supply. This is problematic because we demonstrated that higher-risk prescriptions of greater than 225 MMEs could still fall within 5- or 7-day supply-limit policies aimed at promoting safer opioid prescribing. The days supplied can be specified by the prescriber according to the start and end date of the prescription, or, if this information is not provided, the pharmacist can calculate this before claim submission according to the brand label dosing instructions. Therefore, the number of tablets dispensed per prescription is subject to manipulation and can be quite variable for the same number of days supplied. Furthermore, the number of tablets is more clinically relevant. Large numbers of tablets are commonly left over after prescriptions for acute pain and surgical procedures and are poorly secured.⁴⁶⁻⁴⁸ Decreasing the number of leftover tablets is critical to reducing diversion and

overdoses.⁴² A promising approach is implementing lower electronic medical record order default opioid quantities (eg, 10 tablets), which was recently shown to significantly shift ED discharge prescribing patterns toward the default quantity.⁴⁹ More research is needed to investigate whether prescribing limit policies should incorporate total MMEs or quantity limits.

In summary, our findings continue to support efforts to keep opioid-naïve patients opioid naïve and to use the smallest quantities of opioid possible when clinically indicated for treatment of acute pain. Prescriptions exceeding 30 tablets of oxycodone 5 mg, or a total of 225 MMEs, were associated with transition to prolonged use 30 to 180 days after an initial encounter for ankle sprain among patients who had not previously filled an opioid prescription. Opioid prescribing for ankle sprains remains common and is highly variable at the state and patient level even though opioids are not first-line treatments for this condition. Given that the number of deaths from prescription and illicit opioids continues to increase, there are multiple opportunities for clinical, health system, and state-level interventions.

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Author affiliations: From the Department of Emergency Medicine, Center for Emergency Care Policy and Research (Delgado, Meisel, Yokell, Perrone), the Department of Medicine, Division of General Internal Medicine (Huang, Polsky), the Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine (Delgado, Hennessy), Center for Health Incentives and Behavioral Economics (Delgado), Penn Injury Science Center (Delgado, Meisel), Leonard Davis Institute of Health Economics (Delgado, Huang, Meisel, Hennessy, Polsky, Perrone), and the Department of Health Care Management and Economics, Wharton School (Polsky), University of Pennsylvania, Philadelphia, PA.

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APPENDIX E1

Online Supplement

eFigure 1 Observed to Expected Opioid Prescribing Rate Ratios by State

eTable 1 Most common first listed medical claim diagnosis in 7 days prior to a subsequent opioid prescription 30 180 days after the index ED visit for ankle sprain among those who filled opioid prescriptions on index visit

eTable 2. Association between MME and Prolonged Use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Corresponds with Figure 4 in manuscript. Model A: area under curve (AUC) = 0.78, Homer Lemeshow $p = 0.76$. Model B: AUC = 0.81, Homer Lemeshow $p = 0.41$.

eTable 3. Association between quantity supplied (adjusted for MME/tablet) and prolonged use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Model A: area under curve (AUC) = 0.79, Homer Lemeshow $p = 0.16$. Model B: AUC = 0.81, Homer Lemeshow $p = 0.97$.

eFigure 2. Association between quantity supplied (adjusted for MME/tablet) and prolonged use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Corresponds to eTable 2.

eTable 4. Association between days supplied (adjusted for MME per day) and prolonged use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Model A: area under curve (AUC) = 0.78, Homer Lemeshow $p = 0.96$. Model B: AUC = 0.81, Homer Lemeshow $p = 0.52$.

eTable 5. Association between days supplied (not adjusted for MME per day) and prolonged use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Model A: area under curve (AUC) = 0.78, Homer Lemeshow $p = 0.97$. Model B: AUC = 0.81, Homer Lemeshow $p = 0.69$.

eFigure 3. Association between days supplied (adjusted for MME per day) and prolonged use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Corresponds to eTable 3.

eFigure 4. Association between days supplied (not adjusted for MME per day) and prolonged use (4 or more new opioid prescriptions between 30 180 days after the initial prescription). Corresponds to eTable 4.

eFigure 5. Sensitivity analysis varying definition of prolonged use based on number of subsequent opioid fills between 30 180 days

eTable 6. Unadjusted rates of prolonged use according to number of prescription fills used to defined prolonged use